

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	§		
	§		
Yoseph SHAALTIEL et al	§	Confirmation No.	1887
	§		
Serial No.: 10/554,387	§		
	§		
Filed: October 25, 2005	§	Group Art Unit:	1652
	§		
For: PRODUCTION OF HIGH	§		
MANNOSE PROTEINS IN	§		
PLANT CULTURE	§		
	§	Attorney Docket:	30570
	§		
Examiner: Delia M. Ramirez	§		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DR. YOSEPH SHAALTIEL UNDER 37 CFR §1.132

I, Yoseph Shaaltiel, am the Chief scientist and E.V.P. R&D of Protalix Ltd. at Carmiel, Israel. My professional specialization is in the field of Plant Genetics and Biochemistry, particularly with regard to plant cell culture and industrial applications of plant cell cultures. I have attached a copy of my curriculum vitae with some of the most recent publications.

I am the inventor of the present invention. I have read the present application and the new and amended claims, as well as the Office Action from the Examiner and the accompanying references. In support of the accompanying Response to this Office Action, I set forth below some important historical data which illuminates some of the unique characteristics of the claimed invention.

In this Official action, the Examiner has rejected claims 154-167 under 35 USC 103(a) as allegedly being obvious over Garger et al. (US 2002/088024) in view of GenBank Accession No. P04062, Boller et al. (US Patent No. 6,054,637) and Frijters et al. (NL-1012782).

Claims 154-167 relate to a recombinant human glucocerebrosidase protein comprising amino acid sequence of the mature human glucocerebrosidase protein (SEQ ID NO: 8) linked at it's C-terminus to the vacuolar targeting signal as set forth in SEQ

ID NO: 2, the protein being glycosylated with at least one exposed mannose residue, at least one alpha (1-3) fucose and at least one xylose. The claimed glucocerebrosidase protein exhibits biological activity, both catalytically and with regard to affinity for, and uptake into human macrophages. Also claimed are plant cells expressing the human glucocerebrosidase, pharmaceutical compositions comprising the recombinant polypeptide glucocerebrosidase, and pharmaceutical compositions comprising the plant cells expressing the polypeptide. The plant cells may be carrot cells, cultured in suspension. Culture conditions resulting in efficient culture growth and high yields of recombinant protein are described in detail in the application.

The following summarizes my position as to the non-obviousness of the invention as claimed, with emphasis on considerations of unexpected results, commercial success, long felt but unsolved need, and failure of others, as set forth in *Graham vs John Deere Co.*, 383 US.

(i) The claimed polypeptide yields unexpectedly improved properties, not present in the prior art

The necessity of complex downstream procedures for elimination of signal peptide sequences, and the need to confirm their accurate removal, is of critical concern for the recombinant expression of human glycosylated polypeptides for therapeutic use, as detailed by Cramer et al (*Curr Topics Microb Immunol*, 1999;240:95-108), who emphasized the need for accurate downstream processing of signal peptides in targeted human recombinant proteins:

"With appropriate signals or fusions it is also possible to target proteins to the lumen of the ER or vacuole...One drawback of this strategy is the complexity of the proteolytic cleavage, particularly since carboxypeptidase was required to remove the C-terminal portion of the albumin protein. A failure to precisely control this situation would result in significant product heterogeneity."(Cramer et al, page 107)

Yet further, Garger et al. has cautioned against vacuolar targeting by native lysosomal amino acid sequences acting as endogenous plant targeting and sorting signals (see Garger et al, [0106]), and relates to such C-terminal sorting signals as responsible for inactivation of recombinant lysosomal enzymes produced in plants (see Garger et al, [0276]). Deletion (truncation) of the C-terminal signals (Garger, [0277]),

was reported to have resulted in improved recovery of the lysosomal enzyme activity from the plant interstitial fluid (see Garger et al, [0277]).

In strong contrast, and as a result of its unique production method in plant cells, the claimed plant-expressed human glucocerebrosidase comprises the mature human glucocerebrosidase amino acid sequence (SEQ ID NO: 8) linked at its C-terminus to the plant vacuolar targeting signal Asp- Leu-Leu-Val-Asp-Thr-Met (SEQ ID NO: 2). Unexpectedly, the retention of the additional, non-native C-terminal peptide targeting sequence does not interfere with the claimed recombinant protein's biological activity, which compares favorably, when measured in vitro, with that of Cerezyme® (see Example 3, "Uptake and Activity....", of the instant specification), the clinical "gold standard" for recombinant glucocerebrosidase. Further, in primate and clinical trials, the claimed, plant-expressed human glucocerebrosidase, having the C-terminal targeting sequence, demonstrated safety, lack of toxicity or immunogenicity, and pharmacokinetics comparing favorably with those of the clinical "gold standard" Cerezyme® (see Aviezer et al, PLoS One, 2009; 4: 4792, attached). In further Phase III clinical trials, taliglucerase alfa, comprising the claimed, plant-expressed human glucocerebrosidase, although bearing the C-terminal plant vacuolar targeting peptide, was demonstrated safe by virtue of the lack of serious adverse events, low rate of antibody formation, absence of induced neutralizing antibodies, and a low incidence of hypersensitivity. Furthermore, a good safety profile and statistically significant reductions in hepatosplenomegaly, as well as improvements in hematological parameters, all of which constituted clinical end points, were observed.

Thus the claimed human glucocerebrosidase, efficiently and economically produced in plant cell culture, and bearing a C-terminal plant vacuolar targeting peptide, is unexpectedly comparable, or superior, to plant-expressed human glucocerebrosidase described by Cramer and her associates (see Radin et al, US 5,929,304, 5.4.2 and Cramer, *supra*), which requires post-production modification, and surprisingly comparable, or superior, to the currently prescribed mammalian-cell based clinical "gold standard" Cerezyme®, in all significant clinical criteria.

(ii) Long-Felt Need and Failure of Others

There are approximately 50,000 Gaucher's patients worldwide. Despite the success of enzyme replacement therapy with glucocerebrosidase in reducing pathological processes and improving clinical presentation, only about 10% of

Gaucher's sufferers have been afforded access to enzyme replacement therapy, due to limitations of cost and availability of Genzyme, Inc.'s Cerezyme® (Imiglucerase).

Cerezyme® is a recombinant human glucocerebrosidase produced in Chinese hamster ovary cells, and requires enzymatic remodeling of the recombinant product's glycan profile to achieve a therapeutically efficient enzyme preparation, raising costs and increasing the already significant complexity of enzyme production in mammalian cells. Cerezyme® had been the sole FDA approved therapeutic glucocerebrosidase available at the date of filing of the claimed invention.

Mammalian cell-based systems require carefully controlled fermentation conditions due to the shear sensitivity of the cells, and to control protein glycosylation which may depend on cell metabolism. Cell growth is slow, post-translational glycosylation patterns may be inappropriate or different from the pattern observed in the native glycoprotein. Furthermore, mammalian cells are prone to contamination by pathogens such as viruses or prions. Still further, scaling-up of cultured mammalian cells to large volumes is difficult and costly, as it may take several or more years to build a 100,000L fermenter for CHO cells, costing \$400 to \$600 million. Because of these huge capital costs, industry has been unable to keep up with the growing demand for recombinant biopharmaceuticals.

In the Summer of 2009, viral contamination forced shutdown of production at Genzyme, Inc.'s facilities, halting the fresh supply of Cerezyme® and resulting in lengthy disruption of supplies to the Gaucher community. Such viral contamination is a known liability of mammalian cell bioreactor operations, and has been a recurring problem in Genzyme Inc.'s recombinant biopharmaceutical production line (see [ScientificAmericanblog](#), June 17, 2009, attached). Resumption of production has been slow, and supplies remained limited for nearly two years after the shutdown (see [UK Gaucher's Association website](#), April 22, 2010).

In order to address these obstacles to efficient, safe and cost-effective mammalian cell based human recombinant enzyme production, it has been suggested that human therapeutic proteins be expressed in plants, which offer greatly simpler and less costly production means, higher eukaryotic cellular pathways and freedom from mammalian pathogens.

However, plant-based glucocerebrosidase production has been attempted, but had not met with success until the present invention. Despite acquiring a patent for

human glucocerebrosidase production in tobacco plants (US 5,929,304 to Radin et al.), neither CropTech, Inc. nor Large Scale Biology, Inc., both of which published methods for transformation of plants with constructs directing expression of human glucocerebrosidase in tobacco, were successful in developing a catalytically active plant-derived human glucocerebrosidase product suitable for clinical trials. In stark contrast to these earlier attempts, the claimed plant-cell derived human glucocerebrosidase has demonstrated biochemical parameters, safety and clinical efficacy equal to, if not exceeding those of the FDA approved, clinical "gold standard", Genzyme's Cerezyme®, as detailed hereinabove.

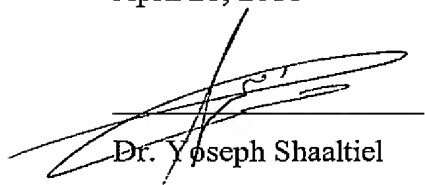
(iii) Commercial Success Derived From the Claimed Invention

As evidenced by the attached press releases, taliglucerase alfa, comprising the claimed plant-expressed recombinant human glucocerebrosidase, has achieved commercial success. On December 1, 2010, the assignee, Protalix Ltd., entered into a marketing agreement with Pfizer, Inc. for the commercialization of taliglucerase alpha. As a result of this widely publicized agreement, Protalix Ltd. has already received \$65 million in up-front payments, and is expected to earn another \$50 million for achieving milestones, based on the claimed invention.

Yet further, on August 10, 2010, Pfizer Inc. entered into a \$30 million short-term supply agreement with the Brazilian Ministry of Health, pursuant to which Protalix Ltd. and Pfizer, Inc. have provided taliglucerase alfa to the Brazilian Ministry of Health for treatment of Gaucher's patients. Revenue generated from the agreement with the Brazilian Ministry of Health will be recorded by Pfizer, Inc., and divided between Pfizer Inc. and Protalix Ltd., according to the terms and conditions set forth in the agreement between Pfizer Inc. and Protalix Ltd.

As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the Application or any patent issued thereon.

April 28, 2011

A handwritten signature in black ink, appearing to read 'Dr. Yoseph Shaaltiel', is written over a horizontal line. The signature is stylized with a large, sweeping initial 'Y' and 'S'.

Enc.: CV of Dr. Yoseph Shaaltiel

Curriculum Vitae

Name: Yoseph Shaaltiel

Permanent Address:

Kibbutz HaSolelim
17905 Doar-Na HaMovil
Israel

Contact details:

Tel: 972-4-988-9488, Ext. 103
Email: Shaaltiel@Protalix.com

Date & Place of Birth:

March 17, 1953, Israel

Professional Experience:

2006-present	Executive Vice President, Research and Development- <i>Protalix Biotherapeutics</i> (former: <i>Metabogal Ltd.</i>)
<i>1996-2006</i>	Director of Research and Development - <i>Metabogal Ltd.</i>
<i>1993-1996</i>	General Manager and Chief Scientist - <i>Metabogal Ltd.</i>
<i>1989-1993</i>	Research associate - <i>Migal Technological Center</i> , Galilee.
<i>1988-1989</i>	Postdoctoral Scholar, B.A.Zilinskas Laboratory, Dept. Biochemistry & Microbiology, <i>Rutgers University, N.J.</i>
<i>1987-1988</i>	Postdoctoral Scholar, B.N.Ames Laboratory, Dept. Biochemistry, <i>University of California</i> , Berkely, CA
<i>1982-1987</i>	Research Student, Plant Genetics Dept., <i>Weizmann Institute of Science</i> , Rehovot, Israel.
<i>1981-1982</i>	Deputy Head, Biology Dept., <i>NBC Center, IDF.</i>
<i>1980-1981</i>	Biochemist, <i>Makor Chemicals Ltd., Jerusalem.</i>
<i>1978-1980</i>	Research Assistant, Dept. Biology, <i>Ben-Gurion University.</i>
<i>1975-1978</i>	Undergraduate research technician, Dept. Biology, <i>Ben-Gurion University, Beer Sheva, Israel</i>

Teaching Experience:

- 1993-1995** *Clinical Biochemistry* for Bachelors degree in life sciences, Emek HaYarden College, under Bar Ilan University supervision.
- 1993-1995** *Biochemistry* for Bachelors degree in life sciences, Emek HaYarden College, under Bar Ilan University supervision.
- 1993-1998** *Chemistry* course for bachelors degree in life sciences, Emek HaYarden College, under Bar Ilan University supervision.
- 1990-1994** *Plant Tissue Culture* course, Biotechnological program, Tel-Hai College.
- 1990-1992** *Scientific Director* of youth scientific summer camp.
- 1989-1993** *Projects Scientific Director* for high school students.
- 1989-1992** *Projects Scientific Director* for biotechnological students, Tel-Hai College
- 1989-1990** *Inorganic Chemistry* course, Hebrew University, Faculty of Agriculture. First year course.
- 1980** *Teaching Assistant, Plant Physiology*, Ben-Gurion University.

Education:

- 1982-1987** *Ph.D. in Plant Biochemistry, Dept. of Plant Genetics, Weizmann Institute of Science, Rehovot.*

Thesis title: Physiology, biochemistry and genetics of resistance to paraquat and other oxidant generating xenobiotics in Conyza and other plant species
Supervisor: Prof. Jonathan Gressel.
- 1983** *ICRO(Special course) , Stockholm.*
The metabolism of xenobiotics and its relationship to chemical carcinogenesis.
- 1979-1982** *M.Sc. in Agriculture, The Hebrew University, Rehovot*
Thesis title: Qualitative determination of polygal acturonase iso-enzymes in different tomato genotypes
Supervisors: Dr. Y. Mizrachi and Prof. N. Kedar.
- 1975 – 1978** *B.Sc. in Biology, Ben Gurion University, Beersheba.*

Fellowships

May-April 1986	British Council Fellowship for research at University of Bath, in laboratory of Dr. A. D
1984-1985	Sephardi Community Fellowship for research at the Weizmann Institute of Science.
June 1983	ICRO fellowship for course at Arrhenius Laboratory, Biochemistry Dept Stockholm University,.

Scientific Publications:

1. Brumshtein B, Aguilar-Moncayo M, García-Moreno MI, Ortiz Mellet C, García Fernández JM, Silman I, **Shaaltiel Y**, Aviezer D, Sussman JL, Futerman AH., **2009**.
“6-Amino-6-deoxy-5,6-di-N-(N'-octyliminomethylidene)nojirimycin: synthesis, biological evaluation, and crystal structure in complex with acid beta-glucosidase.” *Chembiochem*. Jun 15;10(9):1480-5.
2. Aviezer D, Brill-Almon E, **Shaaltiel Y**, Hashmueli S, Bartfeld D, Mizrachi S, Liberman Y, Freeman A, Zimran A, Galun E., **2009**.
“A plant-derived recombinant human glucocerebrosidase enzyme--a preclinical and phase I investigation.” *PLoS One*. 4(3):e4792.
3. Brumshtein B, Greenblatt HM, Butters TD, **Shaaltiel Y**, Aviezer D, Silman I, Futerman AH, Sussman JL., **2007**.
“Crystal structures of complexes of N-butyl- and N-nonyl-deoxynojirimycin bound to acid beta-glucosidase: insights into the mechanism of chemical chaperone action in Gaucher disease.” *J Biol Chem*. Sep 28;282(39):29052-8.
4. **Shaaltiel, Y.**, Bartfeld, D., Hashmueli, S., Baum, G., Brill-Almon, E., Galili, G., Dym O., Boldin-Adamsky SA., Silman, I., Sussman, JL., Futerman, AH. And Aviezer, D. **2007**.
“Production of Glucocerebrosidase with terminal mannose glycans for enzyme replacement therapy of Gaucher disease using a plant-cell system”. *Plant Biotech J* 5:570-590.
5. Yehuda, Y., Goldway, M., Gutter, B., Michael, A., Godfried, Y., **Shaaltiel, Y.**, Levi, B.Z. and Pitcovski, J. **2000**. “Transfer of antibodies elicited by baculovirus- derived VP2 of very virulent IBDV strain to progeny of commercial breeding chickens”. *Avian Pathology* 29:13-19.
6. Pitcovski, J., Goldberg, D., Levi, B.Z., Di-Castro, D., Azriel, A., Krispel, S., Maray, T. and **Shaaltiel, Y.** **1998**. “Coding region of segment A sequence of a very virulent isolate of IBDV - comparison with isolates from different countries and virulence”. *Avian Diseases* 42: 497-506.
7. Pitcovski, J., Di-Castro, D., **Shaaltiel, Y.**, Azriel, A., Gutter, B., Yarkoni, E., Michael, A., Krispel, S. and Levi, B.Z. **1996**. “Insect cell-derived VP2 of Infectious Bursal Disease confers protection against the disease in chickens”. *Avian Diseases* 40:753-761.
8. Gressel, J., **Shaaltiel, Y.**, Sharon, A., Amsalem, Z. **1992**. “Biorational in vitro screening for herbicide synergists”. In: *Herbicide bioassay*. J.C. Strebig and P. Kudsk, Eds. CRC Press, Boca Raton.

9. Jansen, M.A.K., Malan, C., **Shaaltiel, Y.** and Gressel, J. **1989**. "*Mode of Evolved photooxidant resistance to herbicides and xenobiotics.*" Z. Naturforsch 45c:463-469.
10. Jansen, M.A.K., **Shaaltiel, Y.**, Kazzes, D., Malkin S. and Gressel, J. **1989**. "*Increased tolerance to photoinhibitory light in paraquat-resistant Conyza bonariensis measured by photoacoustic spectroscopy and $^{14}\text{CO}_2$ -fixation*". Plant Physiol., 91:1174-1178.
11. Gressel, J. and **Shaaltiel, Y.** **1988**. "*Biorational herbicide synergists*". In: Biotechnology for Crop Protection P.A. Hedin and J.J. Menn, Eds. Amer. Chem. Soc. Symp. Series, 379, pp.4-24.
12. Gaba, V., Cohen, N., **Shaaltiel, Y.**, Ben-Amotz, A. and Gressel, J. 1988. "*Light-requiring acifluorfen action in thabsence of bulk photosynthetic pigments*". Pest. Biochem. Physiol., 31:1-12.
13. **Shaaltiel, Y.**, Glazer, A., Bocion, P.F. and Gressel, J. **1988**. "*Cross tolerance to herbicidal and environmental oxidants of plant-biotypes tolerant to paraquat, sulfur-dioxide and ozone*". Pest. Biochem. Physiol., 31:13-23.
14. **Shaaltiel, Y.**, Chua, N-H., Gepstein, S. and Gressel, J. **1988**. "*Dominant pleiotropy controls enzymes co-segregating with para-quat resistance in Conzya bonariensis*". Theoretica & Applied Genetics, 75:850-856.
15. **Shaaltiel, Y.** and Gressel, J. **1987**. "*Biochemical analysis of paraquat resistance in Conzya leads to pinpointing synergists for oxidant generating herbicides*". Proc. Sixth Int. Cong. of Pesticide Chemistry. Blackwell Scientific Publications, London.
16. **Shaaltiel, Y.** and Gressel, J. **1987**. "*Kinetic analysis of resistance to paraquat in Conzya: evidence that paraquat transiently inhibits leaf chloroplast reactions in resistant plants*". Plant Physiol., 85:869-871.
17. **Shaaltiel, Y.** and Gressel, J. **1986**. "*Multi enzyme radical detoxifying syatem correlated with paraquat tolerance in Conzya bonariensis*". Pest Biochem. Physiol., 26:22-28.

Abstracts and Presentations

- Y. Shaaltiel, 2010** • "*Molecular farming approach for production of recombinant glucocerebrosidase in carrot cells.*" COST ACTION FA0804 Annual Meeting, Naples, Italy
- Y. Shaaltiel, 2008** • "*Plant Cell Culture as a Pharmaceutical Protein Expression System and plant made Glucocerebrosidase*". EU Pharma Law and Regulation conference London,.
- Y. Shaaltiel, 2008** "*Phase II CMC Data for Plant Cell-Made rGlucocerebrosidase*" 5th International BioProcess Technology, Europe • • Amsterdam, The Netherlands
- David Aviezer, Einat Almon-Brill, **Y. Shaaltiel**, Gadi Galili, Raul Chertkoff Sharon Hashmueli,,Tony Futerman Eithan Galun, Ari Zimran **2008**. *Novel Enzyme Replacement Therapy (ERT) for Gaucher Disease: On Going Phase III Clinical Trial with a Recombinant Human Glucocerebrosidase (prGCD) Expressed in Plant Cells* WORLD Lysosomal Research Network Annual Symposium February, Las Vegas, NV, USA

Y. Shaaltiel, 2008, “*Novel and Biogeneric Protein therapeutics*”. The Biotechnology Day, Meitav, Kiryat Shmone, Israel.

A. Zimran, E. Almon-Brill, **Y. Shaaltiel**, Y. Liberman, D. Bartfeld, G. Galili, D. Aviezer, E. Galun **2006** “*A plant cell expressed recombinant human glucocerebrosidase (prGCD) administrated IV: A phase I, non-randomized, open label, single dose-escalation safety study in healthy volunteers*.” 7th International Workshop European Working Group on Gaucher Disease University of Cambridge, UK.

Y. Shaaltiel, 2005 ‘*Expression of biologically active antibodies in an industrial scale plant cell culturing device*’ Plant-Based Vaccines & Antibodies (PBVA June 2005) Prague, Czech Republic

Pitcovski, J. **Y. Shaaltiel**, A. Safadie, M. Malkinson & Y. Weismann **1992** *Computerized image analysis of bursae of fabricius of chickens infected with virulent and vaccine strains of infectious bursal disease virus*. The World's Poultry Science Association The 30th annual convention pp. 30.

Pitcovski, J., **Y. Shaaltiel** and S. Avraham **1990**. *Comparison of structural proteins and antibody production of different isolates of infectious bursal disease virus (Gumboro)*. The World's Poultry Science Association The XXVII -th annual convention pp. 69.

Jansen, M.A.K., **Y. Shaaltiel**, D. Kazzes, and J. Gressl **1990**. *Developmentally controlled co-tolerance to photoinhibitory light and paraquat in resistant and sensitive Conyza bonariensis*. 11th conference of the Weed Science Society of Israel.

N. Cohen, A. Warshawsky, D. Meishar, **Y. Shaaltiel**, J. Gressel. **1990**. *Chelators as synergists to herbicides causing photo-oxidation*. 11th conference of the Weed Science Society of Israel.

Shaaltiel, Y., Jansen, M.A.K., Canaani, O. and Gressel, J. **1989**. Weed Sci. Soc. of America Abstracts.

Shaaltiel, Y., Jansen, M., Glaser, A., Gepstein, S., Warshawsky, A., Cohen, N., Chua, N.-H. and Gressel, J. **1988** 10th conference of Weed Science Society of Israel Phytoparasitica 16:4 367-368

Shaaltiel, Y., Jansen, M., Warshawsky, A. and Gressel, J. **1988**. *Chloroplast mode of evolved photo-oxidant resistance in Conyza*. X Int. Congress of Photobiology, Jerusalem.

Gaba, V., Ben-Amotz, A., Cohen, N., **Shaaltiel, Y.** and Gressel, J. **1987**. *Source of photodynamic activity of acifluorene*. X Israel. Convention of Weed Control.

Shaaltiel, Y., Glaser, A., Gepstein, S., Warshawsky, A., Chua, N.H. and Gressel, J. **1987**. *Resistance to paraquat in Conyza: biochemistry, genetics, controlling resistance by synergism*. X Israel Conv. on Weed Control.

Shaaltiel, Y. and Gressel, J. **1987**. *Resistance to environmental and xenobiotic oxidants: appearance, protection and suppression*. Isr. Bot. Soc.

Shaaltiel, Y. and Gressel, J. 1987. *Copper and zinc chelators synergistic for oxidant generating herbicides.* Weed Sci. Soc. America.

Gressel, J. and **Shaaltiel, Y. 1986.** *Chelators as synergists for oxidant generating herbicides.* Brit. Biochem. Soc., Harden Conference, Wye College.

Gressel, J. and **Shaaltiel, Y. 1986.** *Analysis of mode of paraquat resistance in Conyza bonariensis leads to development of rational synergists for oxidant generating herbicides.* VI Ann. Cong. of Pesticide Chemistry, Ottawa. Abstr. + Poster.

Shaaltiel, Y. and Gressel, J. 1985. *Mechanism of paraquat tolerance in Conyza bonariensis.* Plant Physiol. 77s, 162.

Shaaltiel, Y. and Gressel, J. 1984. *Mechanisms of paraquat tolerance in Conyza bonariensis and in Lolium perenne.* IX Conference Weed Soc. Isr., p. 232.

Mizrahi, Y., **Shaaltiel, Y.** and Arad, S. **1980.** *A method for the separation or identification of endopolysaccharidase isozymes from a crude extract of tomato fruit by means of gel electrophoresis.* Isr. Bot. Soc.

Patents and patent applications:

“Mucosal or enteral administration of biologically active macromolecules” Shaaltiel, Yoseph , Almon, Einat WO2007010533 EP1904638

“System and method for production of antibodies in plant cell culture” Hashmueli, Sharon Shaaltiel, Yoseph Bartfeld, Daniel Baum, Gideon Ratz, Tal Mizrahi, Einat Forester, Yehava WO2006040764 EP1799813,

“Variants of human glycoprotein hormone alpha chain: compositions and uses thereof” - Shemesh, Ronen Shaaltiel, Yoseph Baum, Gideoshalev, Gil Dahary, Dvir Bernstein, Jeanne WO2005044851 EP1682576

“Production of high mannose proteins in plant culture” Shaaltiel, Yoseph Hashmueli, Sharon Bartfeld, Daniel Baum, Gideon Lewkowicz, Ayala WO2004096978 EP1618177

“Cell/tissue culturing device, system and method” Shaaltiel, Yoseph WO2005080544 EP1718726

“Cell/Tissue culturing device and method”. Shaaltiel, Yoseph IL131261, WO9813469 EP0938544 US6391638, JP3987121 HK1023361, MX219063 , PL219063 , IN 193334

“Synergists for herbicidal composition” Israel J. Gressel ,Shaaltiel, Yoseph . IL 77817 WO8704596 EP0258387

“Recombinant Infectious Bursal Disease Proteins and Poultry Vaccines Containing them” Pitkovski, Y.Shaaltiel, B. Levi.. IL 108788